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Radiologic Imaging of Renal Masses

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1. Introduction

Renal cell carcinoma is the third most common urologic malignancy. In the United States in 2010, 58,000 individuals were diagnosed with renal cell carcinoma, of which approximately, 13,000 died. [1] The European Union has experienced a relative increase of 30% for this malignancy over the past two decades. [2] The countries of central and eastern Europe have among the highest recorded incidence of kidney cancers worldwide, with the highest rates observed in the Czech Republic [3] Incidence of this tumor is increasing, the reasons for which are not entirely understood at the current time. Of concern is that despite advances in localized surgical treatment, mortality rates have not decreased.

It is the very nature of this disease that renal masses have long been considered "to be renal cell carcinoma until proven otherwise." The foundation for characterization of renal masses involves imaging. Of critical importance is whether noninvasive imaging can accurately guide diagnosis so as to properly identify those who need intervention, and those, depending on their individual clinical circumstance, who can be safely observed. This goal, which lays at the foundation of research relating to renal masses, has not yet been achieved. Nonetheless, significant advances in understanding of tumor biology have now clarified that renal cell carcinoma is composed of a group of heterogeneous malignancies with distinct genetic abnormalities and natural histories. Advances in imaging technology and techniques has also aided in differentiating benign renal lesions from their malignant counterparts. This new collective understanding of renal masses has given new impetus to more specific characterization of renal masses. This new understanding also allows for a new perspective on the fundamental nature of renal masses that may in turn lead to more precise image based characterization.

1.1 Nature of renal masses

Renal masses are now commonly found as incidental lesions on imaging studies done for other indications. However, review of large series demonstrate that renal masses, notably clinical stage 1 (less than 7.0 cm), are quite heterogeneous. In consideration of this group of renal masses, approximately 20% of them will be benign, with only 20-25% of those that are renal cell carcinoma demonstrating potentially aggressive kidney cancer at time of diagnosis. [4,5,6,7] These renal masses are most commonly diagnosed on abdominal imaging, whether in the form of ultrasound, computerized tomography, or magnetic resonance imaging.

Table 1 summarizes the overall nature of renal masses in the adult population in terms of histological type. Frequency of these lesions is variable, dependant on criteria used for assessing and compiling data. As is the case for many organ systems, though a number of rare uncommon entities are at times found at time of treatment, the focus of the current discussion is on those entities most commonly found. Surgical series may omit patients not candidates for surgery or not desiring intervention. These series may also exclude masses seen on imaging not reaching surgical interventional criteria by the individual investigator. Imaging series may lack complete histopathologic corroboration of all of the lesions noted if not all patients with said lesions underwent treatment where tissue would then be available for histopathologic evaluation. As aforementioned, in many compiled series, notably those focusing on smaller renal masses and associated nephron-sparing procedures, the incidence of benign lesions ranges 20-25%, which is not insignificant.

Renal cyst
Simple
Complex (Bosniak II, III, and, IV)
Cystic nephroma
Adenoma
Oncocytoma
Angiomyolipoma
Nephroblastoma (Wilm’s Tumor)
Transitional cell carcinoma
Renal cell carcinoma
Clear cell
Papillary
Granular
Chromophobe
Collecting duct
Sarcomatoid
Renal medullary
Metastases
Other
Sarcomas
Hemangiopericytoma
Leiomyoma

Table 1. Renal Masses

Nonetheless; patients with advanced symptoms still at time times present with higher stage disease. Larger renal masses (greater than 4 cm) are often malignant forms of renal cell carcinoma and are less of a diagnostic dilemma [9]. Moreover, larger renal masses, regardless of nature, have often already compromised a large portion of underlying renal architecture so as to make any meaningful renal salvage unlikely. In contrast, due to their heterogeneous nature, characterization of small masses is of great importance in that such

image related information can better stratify patients for different management options. It is likely those with relatively small benign tumors can be spared surgical intervention. Those with tumors of low malignant potential, if having concomitant significant medical comorbidity and limited life expectancy may potentially be candidates for active surveillance, and those that are generally considered good surgical candidates, can undergo definitive treatment [10]. Though a large number of well accepted possible surgical interventions, many minimally invasive, now exist for treatment of these masses, these procedures are associated with a degree of patient risk, both in terms of surgical-perioperative risks, and longer term risks associated with potential loss of renal function. To date, there remains question as to overall impact on renal function in procedures where partial nephrectomy takes place under renal ischemia.

1.2 Imaging of renal masses

A number of reports in the radiologic literature suggest that Hounsfield attenuation value and enhancement patterns of renal tumors on computerized tomography may be a valuable non-invasive technique to help distinguish both benign tumors and the different subtypes of renal cell carcinoma. [11, 12] This is already often the case for angiomyolipomas, which due to their fat content, are often readily identified and assigned a radiologic diagnosis. Nonetheless, a small percentage of angiomyolipomas are fat poor, and thus elude diagnosis by this means.

To date, techniques and analyses of computerized tomographic data have generally not provided a reliable means of differentiation between oncocytoma and RCC. However, more recent findings suggest that image based characterization, namely by means of differential enhancement characteristics seen on computerized tomography, may indeed aid in the differentiation of benign and malignant renal masses. [13] This is in part due to newer generation scanners for performance of computerized tomography (CT), which can accomplish more data acquisition-related tasks in a relatively shorter period of time. It is also in part due to looking at the image-related characteristics of these lesions in a new or different perspective.

1.3 Renal tumor characteristics

There are a number of tumor characteristics that may aid in their more specific identification by imaging techniques. Such features include size, location, gross morphology, fat content, degree of vascularity (generally relative to the surrounding normal renal parenchyma), nature of vascularity (i.e. rate that contrast is taken up and eliminated from the tumor), growth rate, and a large number of antigenic/cell specific characteristics which may be amenable to specific radiolabelling. A number of studies have been performed with the aim of identifying clinical parameters that may better suggest the benign or malignant nature of a renal mass. These studies suggest that in addition to smaller tumor size- age, female gender, cystic nature, no associated gross hematuria, non-smoking history, and peripheral nature are all more associated with benign masses. [14, 15, 16] Nonetheless, these clinical findings are without a high enough degree of certainty for confirming or ruling out malignant tumor.

This chapter will explore the unique features of different renal masses and the strengths and weakness of different imaging modalities. As is often the case, different imaging modalities offer a unique perspective on characteristics of any given renal mass. The developing role of

nuclear medicine for detection of tumor through metabolic characteristics will also be explored. Indeed it may be the case that a constellation of image-related findings may be useful for specific non-invasive characterization of a renal mass, and as such may preclude invasive interventions or further guide management for the patient.

The aims of this discussion are to outline the histopathologic and clinical nature of different subtypes of renal masses, to synthesize this information with characteristics of these lesions seen on advanced abdominal imaging, and to shed light on a means for pre-operative, and possibly non-invasive characterization of these lesions. Such information is of great value to patients with renal masses in terms of assessment of overall risk and decision-making.

2. Features of renal cysts, angiomyolipoma, oncocytoma, and renal cell carcinoma

Though there are a relatively large number of different entities that manifest as renal masses in the adult population, the majority that are common in clinical practice are only of a few types, namely renal cysts, complex renal cysts, angiomyolipoma, oncocytoma, and the histopathologic types of renal cell carcinoma. Moreover, little data exists regarding the more rare entities that manifest as renal masses, and as such, the establishment of general principles regarding their nature is not possible at the current time. As such the attention of this discussion is focused on those more common entities.

2.1 Renal cysts

Though the majority of cysts noted on imaging are simple renal cysts, there is a variety of complex cystic masses, which are to a degree indeterminate in nature, as their probability of harboring malignancy is at times difficult to predict. As such, this matter merits significant attention.

Evidence based classification schemes, based on specific image related findings, have been devised in order to help both physicians and patients understand the relative probability that any given cystic mass may harbor malignant renal tumor. Bosniak first introduced his classification of renal cysts in 1986, and has since made refinements in its use. [17] The Bosniak classification system for renal cysts was first developed based on CT findings. However, it has been applied to other imaging modalities; namely ultrasonography and magnetic resonance imaging (MRI). Bosniak did not recommend that ultrasonography be relied upon for differentiation of surgical from nonsurgical complex cystic renal masses. However, he stated that MRI is useful for characterizing complex cystic renal masses because lesion vascularity, manifesting as enhancement, can be evaluated. The Bosniak classification has been applied to MRI in a reliable manner. [18]

The Bosniak classification system has been widely used by both urologists and radiologists due to its clinical practicality. The currently used classification scheme is shown in table 2. [37] Using the lesion's morphology and enhancement characteristics, each cystic renal lesion can be categorized into one of five groups (categories I, II, IIF, III, and IV) each with associated recommendations for patient treatment. [19, 20, 21, 22] Recent modifications include the use of the IIF category. Follow-up study has shown that many lesions that are well marginated, contain multiple hairline thin septa, have minimal smooth thickening of their wall or septa without measurable enhancement, or contain calcifications, which can be thick, nodular, and irregular, are often benign and as such can be followed. [23] Upon follow-up imaging, any further changes in findings for the lesion in question may then

require surgical intervention. Follow-up study has also shown that presence of thick, nodular, and irregular calcification is not as significant as once thought. Rather, it is the presence of associated enhancement that increases risk of malignancy in such lesions. [23, 24]) The critical parameter in the Bosniak classification system is the presence of enhancement, that is to say, presence or absence of tissue vascularity, which generally manifests on imaging as enhancement. The association of this finding with malignant cystic lesions had been the chief reason why many felt that standard ultrasonography alone is not adequate in the evaluation of such lesions. Category III and IV lesions are mainly characterized by enhancement. Nonetheless, with the advent of contrast enhanced renal ultrasound, this issue is now under further investigation.

The goal of the Bosniak classification scheme is to identify those cystic masses with a reasonably high probability of being malignant and thus minimizing the number of benign renal masses that are removed. Category II lesions are generally benign, and can be followed with periodic renal imaging. Statistical probability for malignancy is approximately 50% for category III lesions. Category IV lesions are mostly all malignant tumors. [25]

CATEGORY	DESCRIPTION
I	A benign simple cyst with a hairline thin wall that does not contain septa, calcifications, or solid components. It measures water density and does not enhance.
II	A benign cyst that may contain a few hairline thin septa in which “perceived” enhancement may be present. Fine calcification or a short segment of slightly thickened calcification may be present in the wall or septa. Uniformly high attenuation lesions <3 cm (so-called high-density cysts) that are well margined and do not enhance are included in this group. Cysts in this category do not require further evaluation.
IIIF (F for follow-up)	Cysts that may contain multiple hairline thin septa or minimal smooth thickening of their wall or septa. Perceived enhancement of their septa or wall may be present. Their wall or septa may contain calcification that may be thick and nodular, but no measurable contrast enhancement is present. These lesions are generally well margined. Totally intrarenal nonenhancing high-attenuation renal lesions >3 cm are also included in this category. These lesions require follow-up studies to prove benignity.
III	“Indeterminate” cystic masses that have thickened irregular or smooth walls or septa in which measurable enhancement is present. These are surgical lesions, although some will prove to be benign (eg, hemorrhagic cysts, chronic infected cysts, and multiloculated cystic nephroma), some will be malignant, such as cystic renal cell carcinoma and multiloculated cystic renal cell carcinoma.
IV	These are clearly malignant cystic masses that can have all the criteria of category III, but also contain enhancing soft-tissue components adjacent to, but independent of, the wall or septum. These lesions include cystic carcinomas and require surgical removal.

Table 2. Bosniak classification for cystic renal masses [19]

Biopsy of a renal mass is often entertained as another means to differentiate surgical from nonsurgical cystic lesions, however there are a number of studies that point to the lack of reliability or need for doing so in the majority of cases pertaining specifically to cystic renal masses.[26, 27, 28, 29, 30] Furthermore, although reportedly rare, biopsy of a neoplastic lesion can cause needle tumor seeding and, in cystic masses, potential spillage and implantation of malignant cells.^{14,17} In contrast, biopsy of solid renal masses is quite common, and more so since active surveillance may be a possible management option.

2.2 Renal angiomyolipoma

Angiomyolipomas (AML) are benign neoplasms that, as their name implies, consist of varying amounts of mature adipose tissue, smooth muscle, and blood vessels. [31, 32] It is postulated that angiomyolipomas are derived from the perivascular epithelioid cells.[33] Growth of this neoplasm may be hormone dependent, which is suggested by both its predominance in the female and adult population. [33, 34] 20% to 30% of AMLs are found in patients with tuberous sclerosis syndrome, an autosomal dominant disorder characterized by mental retardation, epilepsy, and adenoma sebaceum (distinctive skin lesion). Of those with tuberous sclerosis, 50% develop renal AML. [33, 34, 35] Renal AML is also more often bilateral and multifocal in this group. In tuberous sclerosis patients renal AML occurs at a 2:1 female: male ratio. [34, 35] In the absence of the tuberous sclerosis complex the lesion occurs more often in female patients, with most patients presenting later in life, during the fifth or sixth decade.[33, 34]

Though non-malignant, renal AML may still be of concern in that they can be associated with serious or fatal hemorrhage. Risk of hemorrhage has been associated with both pregnancy and tumor size. [33, 36]. More than 50% of renal AML are now found incidentally due to more prevalent use of abdominal imaging for the evaluation of a wide variety of nonspecific complaints. [37] On rare occasions these neoplasms may display unusual behavior. Benign AML involving the renal vein and vena cava as a tumor thrombus has been reported. [183]. Further, despite their benign nature, extrarenal occurrences have been reported in renal hilar lymph nodes, retroperitoneum, and liver. Direct extension into the venous system has been reported. A uniformly benign clinical course in such cases has argued in favor of multifocal origin rather than metastasis [33, 38, 32 39]. However, very rare malignant variants of AML have been described.[40, 41] Recent review of this matter suggests that benign AML and more aggressive variants may all arise from perivascular epithelioid cells and that they exist as a spectrum of disease, with the majority having a benign nature. [184, 185]. AML behaving in an irregular manner generally require intense histopathologic scrutiny to ensure proper diagnosis.

2.3 Renal oncocytoma

Literature review suggests that this benign behaving renal histopathologic type represents approximately 3% to 11% of all solid renal masses [42, 43, 44, 45] Mean age at presentation and male-to-female predominance are similar for oncocytoma and RCC, and although oncocytomas are more likely to be asymptomatic (58% to 83%), most RCCs are now also diagnosed incidentally. [46, 44, 42, 47] Mean tumor size for oncocytomas has ranged from 4 to 6 cm in most series-again, similar to RCC. However, giant oncocytomas (16-18 cm) have been reported. [186, 187]. It is important to mind that even very large lesions may be benign, and that if possible, organ sparing surgery should be a consideration. [48, 49, 50, 51]. Familial renal oncocytomatosis is relatively uncommon, but also has been noted.

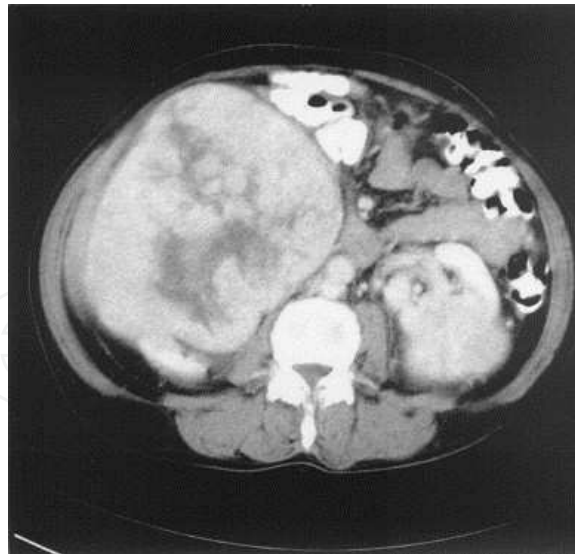


Fig. 1. CT shows 16 x 12 x 15 cm tumor at the caudal pole of the right kidney and 11 x 8.5 12 cm tumor at cranial pole of left kidney. Ponholzer A, Reiter WJ, and Maier U. (2002) Organ sparing surgery for giant bilateral renal oncocytoma. *J. Urol*; 2002: 2531-2532.

In gross appearance, renal oncocytomas are light brown or tan, homogeneous, and well circumscribed tumors. Similar to most renal tumors, they are not truly encapsulated. A central scar may be seen in approximately one third of cases [54], but prominent necrosis is generally not seen. [52, 53] Historically, hypervascularity has been thought to be lacking [52, 53], but these lesions often enhance intensely on contrast enhanced imaging. Oncocytomas cells are packed with numerous large mitochondria, which contributes to their distinctive staining characteristics. Hemorrhage is found in 20% to 30% of cases [44, 54]. Extension into the perinephric fat has also been reported in 11% to 20% of cases, [46, 54] however this is most often not the case in the smaller such lesions that have been resected in recent series. A transitional histopathologic type has been described in the Birt-Hogg-Dubé syndrome, in which renal oncocytomas, chromophobe renal cell carcinoma, and distinctive cutaneous lesions often develop [55]. These transitional neoplasms exhibit features of both oncocytoma and chromophobe RCC, and some authors have hypothesized that there may be a spectrum of tumors spanning both of these histopathologic types [55, 56, 57].

It has long since been known that renal oncocytomas often manifest atypia. However, it has been realized that “atypical” features are part of the renal oncocytoma morphological spectrum and do not appear to affect tumor behavior adversely. [54] Indeed the dilemma of oncocytoma relates to these atypia and its apparent relationship with chromophobe renal cell carcinoma. To date, considerable debate still exists in cases where both of these entities are present. Morphology is often used as the standard. There are a number of reports documenting the coexistence of renal cell carcinomas, not limited to chromophobe RCC, in primary oncocytomas. Though two studies from two referral centers reported a co-existence of 10%-32% [58, 59], a larger number of studies report this incidence to be 0 to 7.2% [54, 60, 61, 62, 63, 64]. This same issue limits the utility of fine-needle aspiration or biopsy [43, 50, 51]. It is possible that evolving molecular and immunohistochemical techniques may further aid in clarification of this issue. Historically, most renal oncocytomas cannot be differentiated from malignant RCC by clinical or radiographic means [65].

2.4 Renal cell carcinoma

Renal cell carcinoma is the most lethal of all urologic cancers, with more than 40% of patients with this malignancy dying of their cancer. It accounts for 2% to 3% of all adult malignant neoplasms. [66, 67, 190] There is a male-to-female predominance of 3:2 [66]. Renal cell carcinoma is primarily a disease of elderly patients, presenting in the sixth and seventh decades of life [67]. The majority of cases of RCC are believed to be sporadic; the United States National Cancer Institute estimates that only 4% are familial. A number of familial conditions associated with renal cell carcinoma are described in the literature. Incidence rates are 10% to 20% higher in African Americans for unknown reasons [68, 190].

The incidence of RCC has increased since the 1970s by an average of 3% per year. This appears in part to be due to the more prevalent use of abdominal imaging for the evaluation of a variety of abdominal, gastrointestinal, and other nonspecific complaints [68]. This trend has correlated with an increased proportion of incidentally discovered and localized tumors and with improved 5-year survival rates for patients with this stage of disease [67, 69]. However, other factors must also be at play because Chow and colleagues [68] have documented a steadily increasing mortality rate from RCC per unit population since the 1980s, and this was observed in all ethnic and both sex groups [191].

Most sporadic RCCs are unilateral and unifocal. However satellite lesions are known to occur, and are often small and difficult to identify by preoperative imaging, intraoperative ultrasonography, or visual inspection; they appear to be the main factor contributing to local recurrence after partial nephrectomy. [70, 71] Bilateral involvement can be synchronous or asynchronous and is found in 2% to 4% of sporadic RCCs, although it is considerably more common in patients with von Hippel-Lindau disease or other familial forms of RCC. [56, 72, 73]. Multifocal disease, which is found in 10% to 20% of cases, is more common in association with papillary histology and familial RCC. [74, 75]

All RCCs were traditionally thought to arise primarily from the proximal convoluted tubules, and this is probably true for most clear cell and papillary variants. However, more recent data suggest that the other histologic subtypes of RCC, such as chromophobe and collecting duct RCC, are derived from the more distal components of the nephron. [76, 77, 78] As of recent, urologic researchers have recognized the distinct nature of the various histopathologic subtypes of RCC through advances in molecular genetics, which has greatly aided in their proper classification. [72]

All RCCs are, by definition, adenocarcinomas, derived from renal tubular epithelial cells [78, 53, 79]. Most RCCs share ultrastructural features, such as surface microvilli and complex intracellular junctions, with normal proximal tubular cells, and they are believed to be derived from this region of the nephron [73]. All of these recent developments indicate that RCC is not a single malignant neoplasm but rather comprises several different tumor subtypes, each with a distinct genetic basis and unique clinical features.

Most RCCs are round to ovoid and circumscribed by a pseudocapsule of compressed parenchyma and fibrous tissue rather than a true histologic capsule. RCCs commonly consist of yellow, tan, or brown tumor interspersed with fibrotic, necrotic, or hemorrhagic areas; they are generally not uniform in gross appearance. Cystic degeneration is found in 10% to 25% of RCCs and appears to be associated with a better prognosis compared with purely solid RCC [88, 89, 90, 91, 190]. Calcification can be stippled or in plaque form, and is found in 10% to 20% of RCCs. Aggressive local behavior is not uncommon with RCC and manifests in a number of ways. Invasion and penetration into the collecting system or renal capsule are found in approximately 20% of cases, although displacement of these structures

is more commonly seen. Further local spread to involve adjacent organs or the abdominal wall is often precluded by Gerota's fascia, although some high-grade RCCs may penetrate this barrier. A notable feature of RCC is its occasional involvement of the venous system, which is found in 10% of RCCs, more often than in any other tumor type. [92, 93]

RCC TYPE	PREVALENCE	ORIGIN	KEY FEATURES
Clear cell	70-80%	Proximal tubule	Hypervascular, aggressive behavior common, most likely to have sarcomatoid features
Papillary	10-15%	Proximal tubule	Hypovascular, multifocality is common
Chromophobe	3-5%	Cortical portion of the collecting duct	Prognosis better than conventional Some aggressive variants
Rare Collecting duct Medullary Unclassified	< 1%	Collecting duct Calyceal epithelium	Infiltrative, generally aggressive Infiltrative, generally aggressive, patients with sickle cell trait Generally aggressive

Table 3. Subtypes of renal cell carcinoma [55, 72, 73, 76, 80, 79]

RCC has long been recognized as one of the most vascular of cancers as reflected by the distinctive neovascular pattern exhibited on renal angiography. Unlike upper tract transitional cell carcinomas, most RCCs are not grossly infiltrative, with the exception of collecting duct RCC and some sarcomatoid variants. [73] Tumors smaller than 3 cm were previously classified as benign adenomas, but some small tumors have been associated with metastases, and most pathologists agree that with the exception of oncocytoma, there are no reliable histologic or ultrastructural criteria to differentiate benign from malignant renal cell epithelial tumors [73].

The vascular nature of RCC plays a special role in imaging of this tumor. Various studies have tried to differentiate between the clear cell and papillary subtypes of RCC based on the degree of enhancement on contrast-enhanced CT as well as MRI. As a general point, a number of these studies have shown excellent accuracy, with higher early enhancement in clear cell renal cancers. [94] In addition, clear cell RCC has a strong association with necrosis and retroperitoneal collateral circulation that is best seen on MRI [95]. On the other hand, papillary RCCs show homogeneous low-level enhancement on both CT and MRI [94, 96]. This will be discussed in detail for each type of imaging modality.

The indications for percutaneous renal biopsy or aspiration in the evaluation of solid renal masses have traditionally been limited, primarily related to concerns about sampling error, difficulty interpreting limited tissue given the inherent similarities between the eosinophilic variants of RCC and oncocytoma, and recognition of the improved diagnostic accuracy of cross-sectional imaging such as CT or MRI. [82, 83] Eighty-three percent to 90% of solid renal masses thought to be suspicious for RCC based on careful radiographic evaluation prove to be RCC on final pathologic analysis [84]. Fine-needle aspiration biopsy (FNAB) cannot significantly improve on this degree of diagnostic certainty and is unlikely to influence clinical management in the majority of cases [27, 85]. More recently, FNAB has been reassessed, and several groups have shown enthusiasm for this approach. Some

studies suggest improved sensitivity and specificity, particularly when FNAB is combined with molecular analysis for CA-9 expression or other markers for RCC. Molecular analysis could also assess HMB-45 expression to evaluate for atypical AML, and genetic analysis for oncocytoma may also be available in the near future. In addition, FNAB could influence clinical management of small renal masses if markers of clinical aggressiveness could be established and reliably evaluated on limited pathologic material. The potential complications of FNAB include bleeding, infection, arteriovenous fistula, needle track seeding, and pneumothorax. [82] In general, the incidence of complications has been reduced significantly since the introduction of smaller gauge needles. Tumor location, operator expertise, and number of biopsy attempts can also influence complication rates. Perinephric bleeding can be detected by CT scan in 90% of cases, but clinically significant hemorrhage resulting in gross hematuria is much less common (5% to 7%) and is almost always self-limited [86, 87]. Only five cases of needle track seeding have been reported with RCC. Overall, the estimated incidence of needle track seeding with urologic malignant neoplasms is less than 0.01%; most occur with poorly differentiated transitional cell carcinoma [82].

3. Imaging modalities

Anatomic imaging modalities historically used for the characterization of renal masses include intravenous contrast-enhanced plain film radiography, ultrasonography, computerized tomography, and magnetic resonance imaging. Imaging via nuclear medicine and hybrid nuclear medicine/computerized tomography techniques has also emerged.

Plain film radiography and computerized tomography require use of ionizing radiation. Advances in radiation technology and equipment design have resulted in lower doses and overall exposure, but total exposure is additive. Total exposure to ionizing radiation for a patient is of consideration, as there are carcinogenic risks associated with exposure to large cumulative doses of radiation. Total radiation exposure is measured in a number of different manners. Doses may be measured as both skin doses and total effective radiation dose. Effective absorbed radiation, in Sieverts, can also be measured. Cumulative evidence from a number of studies suggests that three-phase CT scan exposes patients to approximately two to three times as much radiation as approximately 12 plain film radiographs (though not that many be required) taken during the course of intravenous pyelography (IVP). [97, 98, 99] More advanced CT protocols, namely multiphase protocols, have made this issue of more significant concern. Possibilities for limiting radiation in these studies include eliminating a phase (which may then limit examination accuracy) or reducing mA during some of the phases of the study. [100] At the current time, low dose CT protocols are being investigated, primarily in the setting of urinary lithiasis, with a focus on maintaining diagnostic accuracy while decreasing exposure. Patients of higher body mass index may not be ideal for low dose CT [101]. Newer subtraction techniques may also allow for fewer runs through the scanner

Intravenous contrast-enhanced plain film radiography and computerized tomography both also involve the use of intravenous iodinated contrast agents, which carry an albeit low, but real risk. Iodinated contrast media entail risk in three manners: (1) metabolic effect relating to their hypertonicity, (2) inducement of acute renal dysfunction, and (3) idiosyncratic contrast material reactions.

Risks associated with hypertonicity include increased cardiac output and decreased peripheral vascular resistance due to volume expansion [102], inhibition of the coagulation cascade by high osmolar contrast agents [103], and renovascular dilation followed by renovascular constriction, with a result decrease in glomerular filtration rate. [104]

Acute impairment in renal function (increase in serum creatinine of 0.5 to 1.0 mg/dl or 25-50% decrease in GFR) occurs in 1/1,000-5,000 patients without known risk factors. This condition is generally nonoliguric, however, when it is accompanied by oliguria, risk of permanent renal damage exists. [105, 106] Risk factors increasing the risk of acute renal dysfunction include dehydration, pre-existing renal insufficiency, diabetic nephropathy, congestive heart failure, hyperuricemia, proteinuria, and multiple administrations of contrast material in a short time period. [107]. General recommendations to avoid acute renal dysfunction include ample pre-examination hydration, avoidance of dehydrating preparations, and a reduction in total contrast used, if feasible.

Patients taking metformin for control of diabetes mellitus are advised to stop this medication 48 hours prior to contrast administration. When renal function and urine output are demonstrated to be normal after imaging, metformin therapy may be resumed. The concern for these patients is that if acute renal dysfunction occurs during metformin administration, these patients may develop significant lactic acidosis. [108]

Idiosyncratic contrast material reactions may occur in mild, moderate, and severe forms. Mild reactions include metallic taste, sensation of warmth, sneezing, coughing, and mild urticaria. Moderate reactions include vomiting, more severe urticaria, headache, edema, and palpitations. These reactions can be symptomatically treated as needed. However, severe reactions, which include hypotension, bronchospasm, laryngeal edema, pulmonary edema, and loss of consciousness, require immediate intervention. Severe reactions occur in less than 0.1% of patients, and it is estimated that 80% of these may be avoided by use of low osmolar contrast media. [109, 110]

All contrast-associated risks appear to be lowered by use of low osmolar contrast media currently available. Administration of prophylactic corticosteroids and use of low osmolar contrast media have been shown to decrease the risk of contrast reaction, but not eliminate it. [111] Methylprednisolone 32 mg oral may be given every 12 hours starting 24 hours prior to examination. This is continued 12-24 hours after the examination to ensure that all contrast material has been excreted. [112] Diphenhydramine 50 mg oral may also be administered before contrast administration. All patients offered intravenous iodinated contrast studies should be counseled and informed of these associated risks.

Many imaging studies relate to differentiation of benign and malignant lesions. Nonetheless they will be presented in the following where they relate best to the discussion.

3.1 Contrast-enhanced plain film radiography

The IVP, or intravenous pyelogram (also IVU-intravenous urogram) had long been a mainstay of urologic diagnostic imaging. This test requires use of intravenous iodinated contrast. IVP generally requires bowel preparation for optimal imaging results, an absence of patient contraindications to intravenous iodinated contrast administration, repeated imaging over thirty to sixty minutes, and at times more prolonged imaging if renal obstruction is present.

After a scout film is taken, contrast is injected, at which time nephrotomograms are obtained. These images may reveal abnormalities of the renal parenchyma. However recent

studies comparing IVP to other imaging modalities, namely computerized tomography, show that sensitivity for detection and characterization of renal masses is limited. [113] Findings suggestive of a mass seen on IVP generally require other types of imaging for both corroboration and specific delineation.

IVP may provide valuable information pertaining to the pyelocalyceal system, including the existence of hydronephrosis, hydroureteronephrosis, existence of urinary stones, and “filling defects” which include a variety of diagnostic possibilities. However, IVP has limited sensitivity for renal parenchymal pathologies. Previous studies have documented the limited sensitivity of small renal masses, particularly when masses are less than 3 cm [113, 114, 115, 116]. CT urography has gained great popularity in that it provides reliable assessment of both the renal parenchyma and collecting system. A prospective comparison of contrast enhanced CT and IVP in initial evaluation of microscopic hematuria demonstrated that examination with CT had better diagnostic yield for a wide variety of pathologies. [113]

IVP has fallen out of favor at many institutions for a variety of reasons that include; risk of contrast toxicity, time consumption involved in performance of test, and limited diagnostic accuracy in triage setting where diagnoses are often still uncertain. In many institutions it is now only rarely performed.

3.2 Ultrasonography

Ultrasound requires neither iodinated or gadolinium-based contrast administration, nor ionizing radiation. Its mechanism of action is based on the transmission of a pulse of high frequency sound energy into the patient. These sound waves are then reflected, refracted, or absorbed, depending on type of tissue encountered. The ultrasound transducer also acts as a receiver, which receives the returning echoes. Collected input is processed by a computer for the creation of a composite image. [117] Ultrasound is performed in a real time manner which allows for the technician and physician to modify and review different aspects of the examination. Newer machines also have significantly improved resolution.

Ultrasonography is used widely throughout medicine. It may be used by anyone with proper training and experience in almost any clinical scenario; radiology suite, emergency room, clinic, and under sterile conditions in the operating room. The applications of ultrasonography are so extensive that they are beyond enumeration here. However, it is of critical importance to understand that imaging performed with this modality is operator-dependent. This generally requires that the interpreter of the study be present during the actual real-time study. Image quality is also closely related to the quality of equipment being used.

Ultrasonography is performed with use of a variety of probes depending on parameters that include patient body habitus and structures to be imaged. In the case of the kidney, 3.5 to 5 MHz transducers are typically used. Transducers of this range are used to obtain adequate depth of penetration without substantial loss of resolution. Bony structures and bowel gas may both interfere with renal imaging, more so on the left than the right.

Ultrasound is commonly employed as an initial imaging exam due to its relative low cost, relative ease of performance, and lack of need for ionizing radiation. The strength of ultrasonography is its ability to differentiate solid versus cystic renal structures. In the hands of an experienced ultrasonographer, it is quite reliable for the identification and confirmation of simple renal cysts. Historically, there has been concern regarding low sensitivity for detection of small renal masses. [114, 116] However there is evidence that well

performed duplex ultrasonography may be highly accurate in the diagnosis and staging of a large number of renal masses, including those cases where renal vein or caval thrombus are involved. As active surveillance has become an option for select patients with renal masses, type of surveillance imaging has become an important issue. A recent study comparing size of renal masses noted on US, CT, and MRI, comparing imaging results to final pathology, demonstrated all three modalities accurately predicted pathologic tumor size. This study included relatively small renal masses as well. [118] However, there may be limitations with use of ultrasound in respect to the identification of lymphadenopathy. [119]

Renal ultrasonography also has a large role in imaging in patients with azotemia, those with severe contrast allergy, pregnant patients, neonates, and children. Ultrasonography may at times be quite useful for assessment of renal masses in the intraoperative setting, both for open cases and laparoscopic cases. In the open setting it may be useful for the identification of relatively small masses completely hidden within the renal parenchyma, or in cases where multiple small tumors, not all of which are immediately amenable to manual palpation, are suspected. Laparoscopic ultrasound may be useful in a similar fashion, and may also be used in concert with different ablative devices that are at times used in the treatment of select renal masses. [120]

3.2.1 Advances in ultrasound technology and technique

Concerns with use of renal ultrasound for detection of renal masses is noted from earlier data showing that renal masses 3 cm and less are detected only 67-79% of the time. [121]. One must consider that renal tumors may at times have similar echogenicity to normal renal parenchyma. However, with improvements in ultrasound technology, namely in terms of resolution and Doppler technology, this may no longer be the case. More recently, contrast-enhanced ultrasonography (CEUS) has been introduced as another means of further characterizing renal masses. Ultrasound contrast agents (gas filled microbubbles covered by a stabilizing shell) are injected as liquids, and then manifest as a gas when in the bloodstream. This contrast agent, in its gas form, improves the detection of Doppler signals and helps better reveal both normal and abnormal vascularity. [122] At time of performance of the study, the contrast agent is injected, and when evident on imaging, the patient holds their breath while a number of ultrasound frames are obtained for analysis. CEUS entails less risk than contrast-enhanced computerized tomography, can show even subtle tumor blood flow, and may serve as a viable alternative for patients unable to undergo contrast enhanced CT or MRI for any variety of reasons. [123] In study of complex cystic renal masses CEUS has shown to be comparable in characterization of such masses with use of the Bosniak system. [124, 125] CEUS may also improve visualization of renal vessels, detection of vascularity in solid renal masses, and detection of vascularity in septa and walls of complex renal masses. [126, 127, 128] Use of microbubbles in this manner has been shown to have a high safety profile, with incidence of adverse reactions lower than that observed for iodinated and gadolinium based contrast agents.[129]

3.2.2 Ultrasonography and differentiation of renal masses

Angiomyolipomas most often are associated with distinct radiographic findings, which generally relate to their fat content. The typical but not diagnostic finding of AML on ultrasonography is a well-circumscribed, highly echogenic lesion, often associated with shadowing. [37, 25] The finding of shadowing should suggest an AML rather than a small,

echogenic RCC, which rarely shadows [25]. In terms of differentiation and characterization of solid renal masses using ultrasonography, the presence of shadowing, a hypoechoic rim, and intratumoral cysts are thought to be important findings that may help distinguish angiomyolipomas from other solid lesions, namely renal cell carcinoma. [130] Nonetheless, these findings are not reliable enough to make such a diagnosis with reasonable certainty. Although conventional ultrasound has not resulted in more specific characterization of renal masses in terms of histopathologic type/subtype, this will issue will likely be re-evaluated with introduction of CEUS.

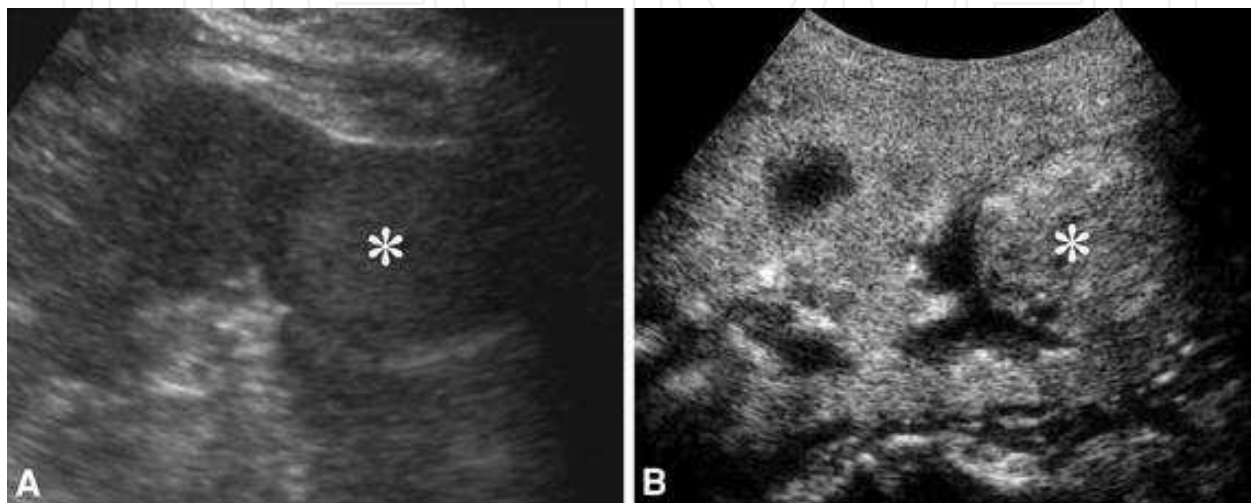


Fig. 2. Renal tumor at the lower pole of the right kidney. Transverse scans. a. A well-defined expansive, hyperechoic mass is observed at grey-scale ultrasound. b. The mass shows intense enhancement at CEUS. Siracusano S, Bertolotto M, Ciciliato S, et al (2011) World J Urol. Epub ahead of print.

3.3 Computerized tomography

Sir Godfrey Newbold Hounsfield, (28 August 1919 – 12 August 2004) and Allan MacLeod Cormack (February 23, 1924 – May 7, 1998) shared the 1979 Nobel Prize for Physiology/Medicine for developing the diagnostic technique of X-ray computed tomography (CT). Beyond doubt, the introduction of the CT scanner is a critical point in the evolution of medicine.

Since time of inception, CT has taken an increasing role in the realm of imaging. In 2006, over 60 million CT examinations were performed in the United States. [131] In 2008, over 140 million CT examinations were performed worldwide. [132] Similar to plain film radiography, images obtained by this modality are created due to the attenuation of photons by the body tissue being examined. A thin collimated x-ray beam is generated on one side of the patient. Detectors on the opposite side of the patient then measure the amount of transmitted radiation. In any given transverse plane being examined these measurements are repeated as the x-ray beam rotates around the patient. During processing, the measurements are taken and placed into a matrix of CT values that correspond to attenuation of a given tissue volume within the patient. The gray scale of each CT pixel is related to the amount of radiation absorbed at that point. This value is called the attenuation value, and is commonly denoted in Hounsfield units. Clinically relevant CT Hounsfield unit values are shown in table 3. [133, 117]



Fig. 3. Sir Godfrey Newbold Hounsfield, (28 August 1919 – 12 August 2004) standing beside early CT scanner. Source: unknown

Absorber	CT numbers (HUs)
Bone	+1000
Calculus	+400 or greater
Calcification	+160 OR GREATER
Acute hemorrhage	+50 to 90
Soft Tissue	+10 to 50
Water	0
Fat	-100
Air	-1000

Table 4. Hounsfield Values [133]

Obtained measurements are then taken from a given transverse slice of body tissue and are mathematically processed by a computer that then reconstructs a cross-sectional image of the body. Early CT scanners obtained transverse images one slice at a time. However, later generation spiral (or helical) CT scanners allow patient movement on a gantry with simultaneous tunnel rotation with continuous x-ray exposure. This arrangement allows for rapid acquisition of volumetric data from the patient being examined during the time in which breathing is suspended. The acquisition of volumetric data is of great value in terms of renal imaging in that it allows for greater accuracy and detail in terms of evaluating renal parenchymal masses and renal vasculature, particularly in terms of visualization of small renal masses and supernumerary renal blood vessels. Studies have indeed shown that thin slice overlapping reconstructions are quite useful for differentiation and accurate depiction for renal masses as small as 5 mm. [188]) Data acquired in this manner also allows for high quality CT angiography and three dimensional reconstructions in a variety of manners. [117]

Contrast enhanced computerized tomography provides excellent anatomic detail for retroperitoneal structures and has become the primary imaging modality for renal masses. Distinct phases have been clearly identified for patients undergoing intravenous contrast-enhanced renal imaging. These phases include the arterial, corticomedullary, nephrographic, and excretory. The arterial phase occurs approximately 15-25 seconds after contrast administration. It is most useful for identification of renal arterial anatomy, evaluating potential renal donors, and those with suspected renovascular pathologies. The corticomedullary phase occurs approximately 25-70 seconds after injection. During this phase the renal cortex has intense enhancement, as glomerular filtration of the contrast material begins to take place. This phase is useful for the identification of hypervascular renal tumors, notably clear cell renal cell carcinomas. The renal veins can also be seen well during this phase. The nephrographic phase generally occurs 80-120 seconds after contrast administration. During this phase contrast has been filtered through the glomeruli and has made its way to the collecting ducts. During this phase the renal parenchyma appears homogenous. It is at this time that subtle renal parenchymal masses are best detected. The last phase, the excretory phase generally occurs 180 seconds after contrast administration. During this phase the renal calyces, pelvis, and ureters are opacified. Further delayed imaging may be necessary to ensure that all portions of the ureter have been opacified. [134] Advanced protocols for contrast enhanced computerized tomography have been employed with the intention of gathering as much data as possible in examination of a renal mass. These protocols are directed toward differentiation of hyperdense cysts, complex cysts, and various types of solid renal masses i.e. oncocytomas, angiomyolipomas, and subtypes of renal cell carcinoma. These protocols often entail the identification of a region of interest within the mass in question, and then recording its density, in Hounsfield units, throughout the various phases of the study, which include the noncontrast phase, and the aforementioned contrast enhanced phases. Understanding the nature of multiphase CT is of critical importance in that enhancement is the most important factor in determining likelihood of malignancy. Furthermore, it appears that enhancement, which appears to be representative of the degree of angiogenesis, or vascularity within a tumor, also correlates to a degree with renal cell carcinoma tumor subtype [189]. CT enhancement is generally defined as an attenuation increase of at least 15-20 Hounsfield units (HU) from the corresponding noncontrast image. Lesions showing HU increases of 10-20 are not definitely categorized as enhancing masses due to a phenomenon known as cyst pseudoenhancement. As such, it is at times difficult to discern hypovascular lesions, such as papillary renal cell carcinoma from benign renal cysts. [135, 136] Though not exclusively specific, certain types of renal masses tend to have relatively common features on multiphase computerized tomography. Angiomyolipomas often have fat components, which appear as low attenuation regions (generally negative Hounsfield units) seen best in the unenhanced phase. Histological subtypes of renal cell carcinoma generally are vascularized to different degrees, and may have characteristic enhancement "signatures" on multiphase contrast enhanced computerized tomography.

3.3.1 Advances in CT technology and technique

CT scanners are undergoing a continuing evolution. Newer generation scanners have larger numbers of detectors that exist in a variety of configurations. Additional detectors also allow for more helices to be generated. The purpose of the multiple detectors is the

acquisition of isotropic data sets, allowing for reformatting in multiple planes with near equal resolution. The most recently produced scanners have 64-256 rows of detectors, which allow for rapid imaging and more precise imaging of smaller masses. This evolution may continue with even newer paradigms of detection that include an image plate detector. It is believed that this new advance may further improve imaging of very small structures, such as small renal masses and small renal blood vessels. Such technology may also result in less volume averaging and pixilation, factors that often limit imaging of complex cystic renal masses and small solid renal masses. [137]

In an attempt to limit radiation exposure, dual energy CT (DECT) has been extensively investigated. This technique involves retrospective removal of iodinated contrast from enhanced CT images, thus potentially eliminating need for the initial noncontrast scan via production of a virtual noncontrast scan. This technique has been applied more extensively to evaluation of urinary stones. However, as of most recent, a feasibility study with use of DECT equipped with a tin filter (for increased x-ray energy spectra separation) has shown improved sensitivity and specificity for discriminating cysts from enhancing masses in phantom models. [138] Early study of application of this technique in relation to renal masses has shown that single phase post contrast DECT, when reviewed in conjunction with the virtual noncontrast data set, had an accuracy of 94.6% in diagnosing malignant renal lesions, in comparison to 96% accuracy with use of multiphase CT examination. The reduction in radiation dose, with use of DECT, was 47%. [139] The full potential of this application will require further investigation.

Another new technique being introduced that may yet broaden the possibilities of tissue imaging with this modality is dynamic contrast enhanced CT, or perfusion CT. This evolving technique has the capability of assessing tissue perfusion in a noninvasive manner. [140, 141] The technique has been used for imaging both the brain and tumors. It may be particularly useful in evaluating tumors that are potentially treatable by antivascular therapies, by evaluating the efficacy of such therapies. As RCC is known for both angiogenesis and vascularity this technique may show promise. To date, perfusion CT has been used to show that highly vascularized metastatic renal tumors are associated with poorer prognosis. [142] However, a feasibility study suggested that perfusion CT provided significant data regarding tumor angiogenesis and histological subtype in primary renal tumors. [143] As such, it is possible that such prognostic capabilities may also be applicable to primary renal tumors.

3.3.2 Computerized tomography and differentiation of renal masses

On computerized tomography AML are generally of low Hounsfield unit attenuation value (-20 HU and less) in the unenhanced phase [37, 144], and have not been found to be associated with calcification as may be the case with renal cell carcinoma. [37, 145] Aneurysmal dilation is found in 50% of AMLs when they are visualized by angiography and can also suggest the diagnosis [37], but irregular vascularity can be seen in cases of renal cell carcinoma as well. However, fat poor angiomyolipomas may not show such features. In 14% of AMLs, fat cannot be identified with CT, presumably related to a reduced proportion of mature adipose tissue, and a definite diagnosis cannot be made. [37, 146] Milner et al noted that cases involving less than 25% fat/high power field on histologic analysis correlated with computerized tomographic findings where fat usually was not noted. [147] MRI However, newer generation CT scanners with improved spatial resolution are also useful for detection small amounts of gross fat not detected on MRI. [148] Otherwise, based

on imaging, indeterminate cases are considered RCC until proven otherwise, which in turn may necessitate surgical intervention. Such lesions are only confirmed to be angiomyolipoma on final histopathological inspection.

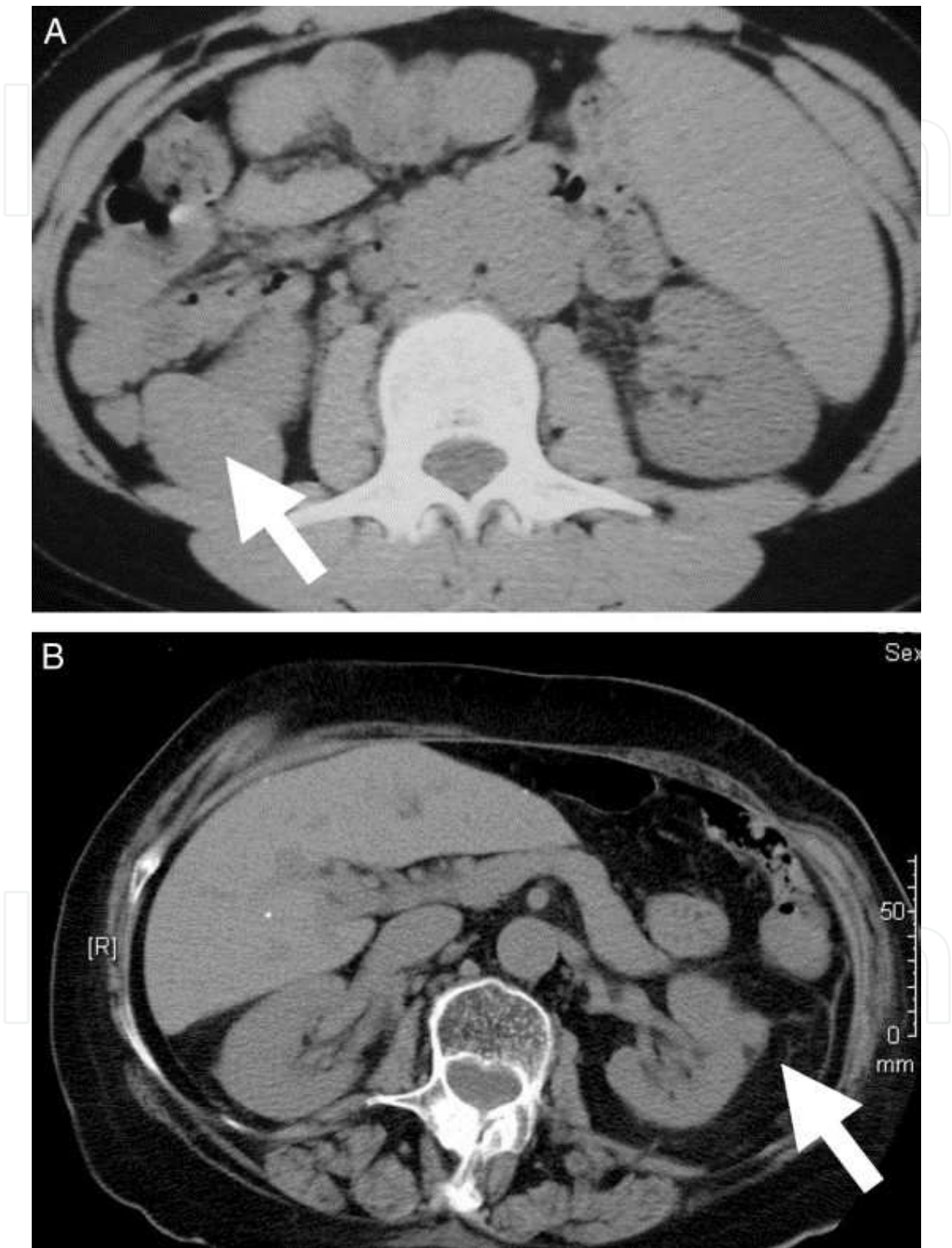


Fig. 4a and 4b. Nonenhanced CT shows hyperdense right (A) and isodense left (B) kidney lesions (arrow). Milner J, McNeil B, Alioto J, et al. (2006) fat poor angiomyolipoma: patient, computerized tomography and histological findings. *J Urol*; 176: 905-909

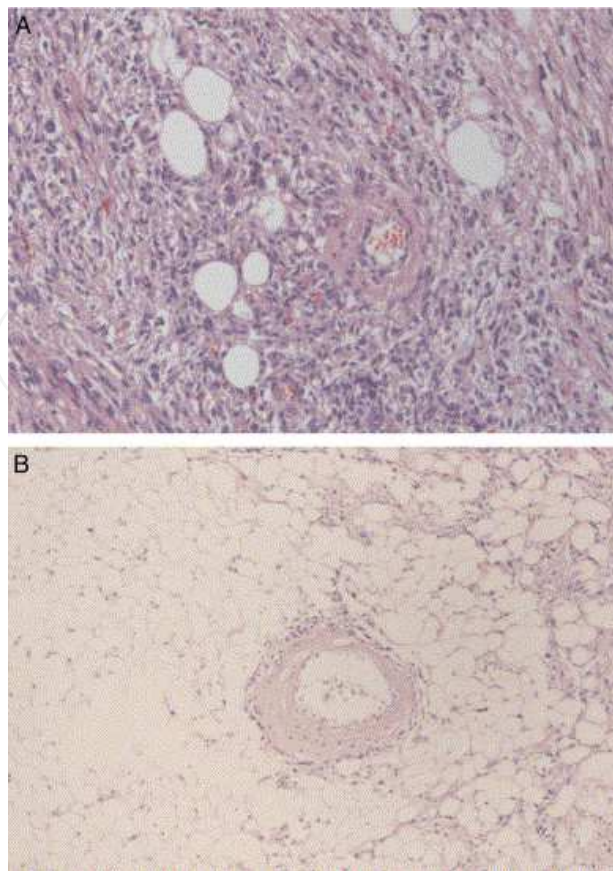


Fig. 5a and 5b. Fat poor lesion (A) with less than 25% fat and classic lesion (B) with greater than 75% fat and percent fat contents. H & E, reduced from x 40. Milner J, McNeil B, Alioto J, et al. (2006) fat poor angiomyolipoma: patient, computerized tomography and histological findings. *J Urol*; 176: 905-909

In a recent retrospective study of enhancing renal masses using dual phase (plain and nephrographic), masses (AML and non-AML) were evaluated with three different size (8-13 mm; 19-24 mm; and 30-35 mm) regions of interest (ROI) over the lowest attenuation value focus of the mass from images obtained in both phases. Different attenuation thresholds were studied and receiver operating characteristic (ROC) curves were derived. At attenuation threshold -10 HU and lower, with use of at least 19-24 mm ROI, on the unenhanced images, was found to be optimal for diagnosis of AML. At this threshold, misdiagnosis rate was 0.5%; at -15 HU threshold misdiagnosis rate was 0%. [149]

Renal oncocytoma is typically described to be a hypervascular, homogeneous mass that may contain a central stellate scar on computerized tomography (CT). However, extended experience has proved these findings to be unreliable and of poor predictive value [48, 49, 50, 51]. However, oncocytomas also appear to be quite vascular, and have a contrast uptake and drainage curve different from that of clear cell renal cell carcinoma.[12] In contrast study, both vascular uptake and washout should be closely examined. Though oncocytomas are considered histopathologically similar to chromophobe renal cell carcinoma, again, their enhance patterns seem to differ (see figure 2).

Enhancement patterns of renal tumors on computerized tomography have evolved to be a valuable non-invasive technique to help distinguish the different subtypes of renal cell carcinoma [150, 151]. Clear cell renal cell carcinomas are often quite vascularized, and often

have high Hounsfield unit values in the early phases of the study immediately following contrast administration. Papillary renal cell carcinomas are relatively hypovascular and generally show mild enhancement during the study. Peak enhancement for papillary renal cell carcinomas may continue to increase during the latter corticomedullary and delayed phases of the study.[12]These different enhancement patterns can be seen in figure 1. Of interest, early investigation in a small number of tumors suggests that chromophobe RCC and oncocytoma may have different enhancement signatures; however, these findings require further investigation and corroboration.

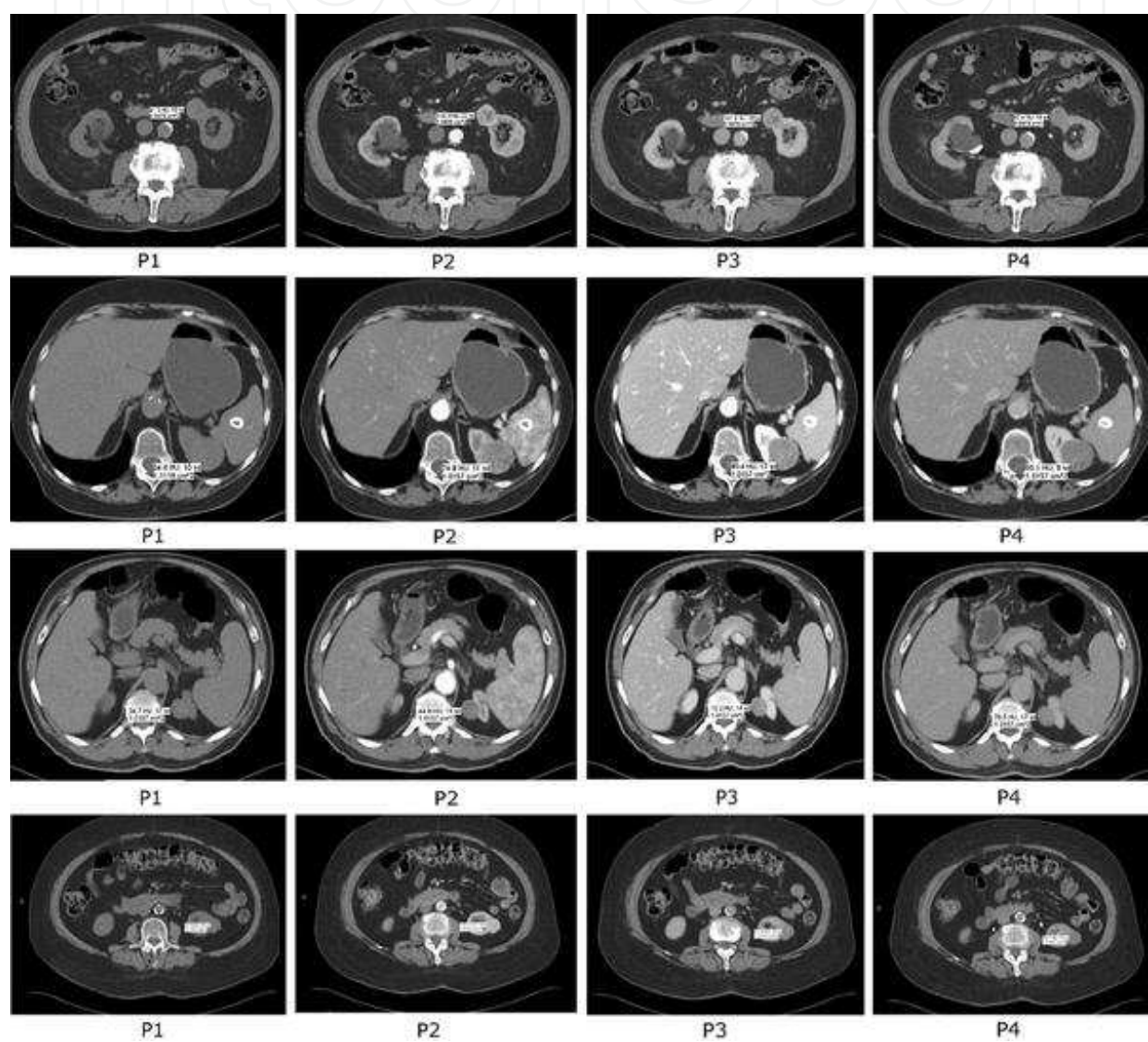
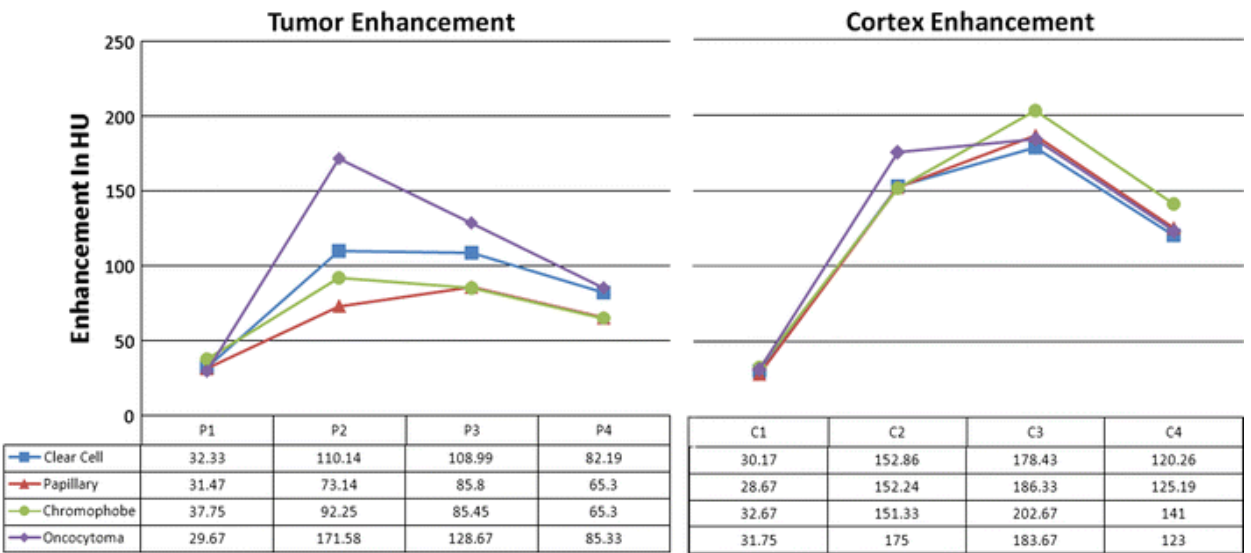


Fig. 6. Plain, arterial, venous, and delayed phase CT images; 1st row-Clear cell RCC; 2nd row-Chromophobe RCC; 3rd row-Papillary RCC; 4th row-Oncocytoma. [11] Bird VG, Kanagarajah P, Morillo G, et al. (2010). Differentiation of oncocytoma and renal cell carcinoma in small renal masses (<4 cm): the role of 4-phase computerized tomography. *World J Urol*; Aug. EPub.



KEY: P1 tumor plain phase, P2 tumor arterial phase, P3 tumor venous phase, P4 tumor delayed phase
C1 cortex plain phase, C2 cortex arterial phase, C3 cortex venous phase, C4 cortex delayed phase.

Fig. 7. Enhancement pattern of renal tumor and renal cortex on 4 phase CT [11]. Bird VG, Kanagarajah P, Morillo G, et al. (2010). Differentiation of oncocytoma and renal cell carcinoma in small renal masses (<4 cm): the role of 4-phase computerized tomography. World J Urol; Aug. EPub.)

3.4 Magnetic resonance imaging

The mechanism of magnetic resonance imaging essentially involves placement of the patient within a magnetic field, which results in the alignment of hydrogen protons in their body tissue. This alignment leads to the formation of a magnetic vector. This vector can be made to spin with application of a radiofrequency pulse. A wire (coil) outside the patient will then have a current induced within it by the magnetic force. The current emanating from the body tissue can then be measured. The magnitude of this current is related to the intensity of the pixel in the MR image. [152] MR information can be processed for creation of direct multiplanar images i.e. transverse, sagittal, and coronal (CT data is acquired in the transverse plane). Due to its nature, MR may yield particularly unique information regarding blood flow and fluid composition, which is useful in a variety of circumstances, namely the identification of fluid and blood in renal cysts and tumor associated renal vein/inferior vena cava thrombus. MR of the kidneys is generally performed on 1.5 or 3 Tesla magnets. The standard sequences used for MR evaluation of a renal mass include T1 weighted imaging (in and out of phase sequences), T2 weighted images in two planes, fat suppressed T1 weighted gradient echo acquisition before and after contrast administration at multiple time points, including arterialcorticomedullary, nephrographic, and urographic phases. [148] Individual institutions also often have slight modifications of this protocol. Acquired MR data can be further analyzed with analysis of subtraction images (subtracting precontrast image from post contrast images). This technique aids in detection of enhancement. In such analyses, areas of high signal appear only in areas of enhancement. [148] In a comparison, for identification of renal malignancy subtraction imaging was more sensitive (99%) when compared to quantitative (quantitative enhancement ratio calculation) evaluation (95%). [153]

Contraindications to performance of MRI include those with pacemakers, ferromagnetic intracranial aneurysm clips, cochlear implants, metallic ocular foreign bodies and some particular makes of older prosthetic heart valves. For MR imaging, breath holding is necessary for proper data acquisition. New generation scanners, with more rapid acquisition times, have allowed for much more practical and reasonable patient breath-holding, however, many a patient has complained about the amount time spent in the confined space of an MR scanner. Open MR scanners are available; however, image quality may be a concern.

For contrast-enhanced MRI, gadolinium, a paramagnetic lanthanide metal, used in conjunction with chelates, acts as the contrast agent. This contrast agent is quite different from iodine based contrast material used in plain film radiography and computerized tomography. It is not specifically nephrotoxic. [154] Gadolinium-based MR contrast agents are associated with less allergic reactions than iodinated contrast agents. [155] It is generally safe for those with a history of allergic reaction to iodinated contrast material. [155, 156, 157] This makes MR imaging attractive for use in the assessment of renal disorders in children, women of childbearing age, and those with renal allografts. [158]

For some time gadolinium enhanced MRI had been an imaging preference for patients with renal insufficiency. However, the use of gadolinium based contrast agents in patients with limited renal function has become a concern. In 1997, a condition, later termed nephrogenic systemic fibrosis (NSF), was noted to occur in a small number of patients undergoing MRI with gadolinium based contrast agents. The condition was first noted in patients with renal failure, and involves progressive fibrosis of the skin and other body tissues. This issue was recently extensively reviewed, delineating the risks of gadolinium exposure in patients with glomerular filtration rate (GFR) less than 30 mL/min. The risk of NSF appears to be very low in patients with higher GFR. [159]

Contrast of different body tissue on MR examination differs from that of CT. Important factors include proton density, T1 and T2 and magnetic susceptibility, and flow. In MR terminology, T1 is a measure of how quickly a tissue can become magnetized and T2 relates to how quickly a given body tissue loses its magnetization. MR protocols for renal masses vary slightly, but essentially include precontrast T1 and T2 fast spin echo sequences, where elements of assessment include discerning the presence of fat (bright T1 signal), hemorrhage (bright T1 signal), and cystic lesions (bright T2 signal). [117] Axial acquisition is preferred as comparison to CT images is often done. Images acquired in the axial plane generally yield the best vascular images as well. Similar techniques are used during the precontrast and contrast-enhanced portions of the exam to allow for proper comparison. Other techniques, such as frequency-selective fat-suppression techniques (FATSAT) or chemical shift (in- and out-of phase) help distinguish the presence of fat from that of hemorrhage in a renal lesion. Specific techniques are also used to assess for flow defects within the renal vein and inferior vena cava. Cardiac synchronized sequence can be used if initial techniques are inconclusive in cases of determination of the presence of renal vein/inferior vena cava thrombus (thrombus results in persistent filling defect over the entire cardiac cycle). [160]

On MR imaging, enhancement is measured in terms of signal intensity. Similar to CT, motion artifact, volume averaging, and fluctuations in signal intensity may result in pseudoenhancement. For a 0.1 mmol/kg contrast dose on a 1.5 T MR scanner 15% enhancement over the baseline precontrast signal has been considered 'significant' enhancement, though it is important to understand that this value may not be applicable to other scanners, field strengths, and imaging techniques. [160]

MRI is useful for differentiation of solid renal masses and cysts. Due to reasons related to cost and availability, urologic evaluations with use of MRI are generally reserved for patients with iodinated contrast toxicity, masses still regarded as indeterminate on CT scan, and cases where there is adequate suspicion for renal vein/inferior vena cava thrombus. MR imaging is considered excellent for vascular structures and the liver, and as such is considered both necessary and useful in cases where the possible presence of renal vein and inferior vena cava tumor associated thrombus needs to be assessed. Various MR techniques may be used to assess for fat within renal tumors, however, as is the case with CT, fat poor angiomyolipomas exist and thus make specific radiologic diagnosis of this entity not always certain.



Fig. 8. In this patient with renal insufficiency (serum creatinine 3.5 ng/dl) T2 weighted images of an unenhanced MRI show a complex left renal lesion to be only cystic in nature, and without solid elements. (Courtesy of author)

As has been done with CT scanning, attempts have been made to use differential intensity of signal enhancement with MR imaging in order to aid differentiation of benign versus malignant masses, namely differentiating benign oncocytomas from malignant renal cell carcinomas. Recent investigations protocols focus on reliable differentiation of these two groups of tumors.

Due to concerns of repeated exposure to ionizing radiation, MR may be preferable CT for active surveillance in patient with renal mass who are either poor candidates for surgery or have otherwise elected this option.

3.4.1 Advances in magnetic resonance technology and technique

Some of the latest advances in MR include use of diffusion weighted imaging, which quantifies the thermally induced motion of water molecules (Brownian motion) in tissues. Restriction of water motion or its diffusion is qualitatively or quantitatively evaluated by means of an apparent diffusion coefficient (ADC) measure. [148] This technique appears quite useful in that DWI does not require gadolinium administration and appears to provide

information regarding tumor microenvironment. Malignant masses appear to have lower ADC than benign ones. This is thought to be due to the high cellularity/complex architecture of neoplastic lesions. [161, 162] It has been further noted that higher Fuhrman grade renal cell carcinomas have lower ADC than lower grade lesions. [163]. Diffusion weighted imaging has also been studied in differentiation of solid and cystic lesions. Again, solid lesions have very low ADC, whereas cysts have higher ADC, Bosniak type 1 cysts had the highest ADC. [164]

3.4.2 Magnetic resonance imaging and differentiation of renal masses

A strength of MRI relates to its characterization of fluid filled entities. It is thus not only accurate in terms of identification of simple renal cysts, but is also quite useful in characterization of cystic renal masses, even in cases where limited renal function or other contraindication preclude gadolinium administration. In a study using Bosniak criteria for evaluation of cystic lesions, 10% of cases were upstaged due to features detected on MRI. MRI appears to be quite useful in detecting the presence, thickness, and enhancement of septa. [18, 165]

Fat-suppressed images on MRI may be helpful in difficult cases or when CT is contraindicated for other reasons. MRI is useful in detection of both macroscopic and microscopic fat in angiomyolipomas. Macroscopic fat can be seen on T1 weighted out of phase sequence and often shows a black outline around the lesion that has been termed the "india ink artifact". In one study this artifact was seen in 100% of AML and 4% non-AML lesions [166]. Microscopic fat not seen on CT can also be detected with chemical shift (in and out of phase) imaging. In these cases, signal loss from the in-phase to opposed-phase images may increase diagnostic confidence for fat poor angiomyolipomas. However, one must bear in mind that clear cell type renal cell carcinoma may contain intracytoplasmic lipid glycogen/lipid that may also manifest as a similar signal loss. [148]

In a recent study, the value of MR T2 weighted imaging was evaluated for diagnosis of AML. The investigators analyzed a group of patients who had undergone CT for enhancing mass with no visible fat. Signal intensity and signal intensity ratio were measured. The signal intensity ratios for AML and non-AML were compared and subjected to receiver operating characteristic (ROC) analysis. Results demonstrated significantly lower signal intensity ratio values for AML. Though promising, the study only contained a small number of angiomyolipomas and will require further investigation. [167]

Characteristic findings for oncocytoma on MRI include well-defined capsule, central stellate scar, and distinctive intensities on T1 and T2 images, all of which can suggest the diagnosis but cannot be considered definitive. [168] MR comparison of chromophobe renal cell carcinoma and oncocytoma shows no significant differences. MR study of enhancement patterns of the clear cell, papillary, and chromophobe forms of renal cell carcinoma has been performed, showing some distinctive enhancement patterns for each of the three subtypes, however, no comparison was made to oncocytoma, the benign tumor that is of critical consideration in this differential diagnosis. [94]

Studies also have shown that papillary RCCs are hypointense on T2-weighted imaging, likely due to old blood products, whereas clear cell RCCs tend to be T2 iso- to hyperintense. Though enhancing renal masses are reliably detected on MRI, renal cell tumor subtyping has not been as extensively investigated in a manner similar to that of CT.

4. Nuclear imaging

The general premise of nuclear imaging involves the administration of radionuclide labeled molecules for a specific purpose for assessment of both physiologic and anatomic details that is not obtainable with other radiologic imaging modalities. Information is gathered by a gamma scintillation camera, which now commonly rotate in a number of directions. Studies more functional in nature may show limited anatomic detail, but newer technologies and complex programming have allowed for more advanced integration of physiologic process/function and related anatomy. Radiation exposure with these techniques is minimal, and valuable functional information, and more recently, functional/anatomic information, may be obtained. Nuclear imaging studies have been employed widely throughout medical specialties and offer great potential as further molecular and physiologic aspects of a number of disease processes are better understood.

Nuclear imaging is more often used to assess extent of disease rather than the specific characteristics of primary renal tumor. However, the possibilities employing techniques using this modality are far reaching. Ready procurement of the needed radionuclide and its bound molecule can at times limit availability of this imaging modality.

4.1 Advances in nuclear imaging technique and technology

Research involving potentiating the application of nuclear medicine in specific tumor identification can be seen in the development of radiolabelled aptamers. The premise involves the production of specific receptor binding molecules based on defined nucleic acid sequences that are capable of recognizing a wide array of target molecules. Aptamers can now be readily produced and are stable. These molecules are generally small, as small as 5-10 kDa, and readily penetrate into tumors. Current efforts focus on manipulating the molecular weight of these molecules to achieve optimal balance between low immunogenicity, good tumor penetration/uptake, and renal clearance. [169]

4.2 Nuclear imaging and differentiation of renal masses

The nuclear agent technetium sestamibi is evidently retained in mitochondria, with reported increased uptake in oncocytomas compared with RCC, AML, and renal cysts. The biologic rationale for nuclear scanning is therefore strong, but these results have not been confirmed, and their clinical role or utility has not been developed. [170]

As aforementioned, ultrasonography, computerized tomography, and magnetic resonance imaging are all commonly used in the evaluation and diagnosis of renal masses. However, a common criticism is that they mostly provide a morphometric analysis, are indeed sensitive, but not very specific. Fluorine-18 fluorodeoxyglucose positron emission tomography (F-18 FDG PET) has been used in diagnosis, differential diagnosis, staging, follow-up, therapy planning, and prognostication in a number of malignancies. [171, 172, 173, 174]. The premise of this imaging technique is that malignant tissues have a higher uptake of FDG than do surrounding normal tissues. This is due to higher levels of glucose transporter proteins and glucose transfer in cancer cells. [175, 176]. PET/CT studies are carried out using a PET/CT integrated scanner. The clinical role of F-18 FDG PET in evaluation of renal masses has yet to be determined, partly because of the physiological excretion of FDG through the kidneys, which makes it difficult to visualize the structures and tumors against the high background of FDG. Different studies to date have reported a wide range of sensitivities for F-18 FDG

PET in this role, with sensitivities ranging from 40-94%. [177, 178]. As of most recent, a prospective study done to further evaluate the role of PET/CT in this setting concluded that a positive PET/CT may indicate the presence of renal cell carcinoma, but that a negative study did not rule it out. The authors noted that higher Furman grade and larger tumor sized increased detection of renal cell carcinoma by PET/CT. [179] The authors also noted a false positive result associated with oncocytoma. Previous studies also noted that oncocytomas can yield false positive results on F-18 FDG-PET/CT [21,41]. [180, 181] In a study by Goldberg et al. [182], patients with indeterminate renal cysts were examined and F-18 FDG-PET/CT accurately detected 10 cysts as benign with no false positive results. To date this modality appears to only have a limited role in evaluation of renal tumor but may be useful as an adjunct study where more standard imaging modalities only yield equivocal results. PET scanning may gain a larger role in staging rather than with evaluation of primary tumors

5. Conclusion

Imaging plays a critical role in the evaluation of renal masses. It is most often the deciding factor in determining whether invasive intervention is necessary. As active surveillance has become an option for some patients, the importance of imaging is only heightened. In addition to differentiation of benign and malignant tumors, better imaging is needed for proper noninvasive identification of those neoplasms of low versus higher malignant potential. At the current time, a large body of research now exists relating to their more specific characterization. Multiphase CT characterization of renal masses has been the foundation of this research, though certainly other modalities, notably contrast enhanced ultrasound, dual energy CT, and diffusion weighted MRI also hold promise. New imaging techniques appear to have improved preoperative identification of angiomyolipoma. Renal oncocytomas have eluded reliable preoperative imaging, but new CT data demonstrates that further investigation into the details of these tumors may also make them identifiable preoperatively. As these tumors relate closely to chromophobe renal cell carcinoma, further molecular studies and characterization of these lesions will likely aid in their proper identification and classification. Use of CT imaging, through exploitation of the vascular nature of renal tumors, has opened the door and demonstrated that specific characterization of renal masses by noninvasive imaging is feasible and should be further studied. Despite its advantages in image resolution and quality, research relating to modification of CT protocols so as to limit exposure to ionizing radiation is also of great importance. The new paradigm of PET/CT imaging is in its infancy and may yet show future promise in terms of providing physiopathologic data in addition to anatomic data. Though any one imaging modality has not yet been demonstrated to be entirely reliable for specific and highly reliable characterization of renal masses, in many cases it appears that a combination of these studies may increase diagnostic certainty, or at a minimum, better direct clinicians in identification of patients who may specifically benefit from percutaneous biopsy. Future directions in the study of renal imaging include further minimizing exposure to ionizing radiation and contrast media related toxicity; further manipulation of advanced imaging protocols to differentiate tissue related differences in renal tumors; and further integration of studies that will yield more specific anatomic and physiopathologic information.

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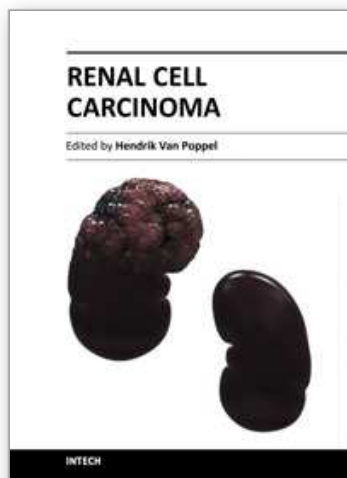
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Surgical and medical oncologists have been unable to decrease renal cell carcinoma mortality for uncertain reasons, although a lot of progress has been made in diagnosis and imaging, recognition of different genetic and pathological entities, management of localized disease and in the research on new drug treatments for advanced stages of the disease, potentially combined with surgery. The purpose of this book, which tackles a number of separate interesting topics, is to provide further insight into the disease and the management of early and advanced renal cell carcinoma. The volume is divided into different parts; the first part covers the characterization of renal masses and the second part covers rare distinct pathological entity. In the management section, active surveillance, partial nephrectomy and radiofrequency ablation are presented. A separate chapter reviews the management of Von Hippel Lindau disease, and finally, conventional and aberrant signaling pathways are explored.

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